REMARKS

Initially, the Applicant has amended the two independent claims, Claims 40 and 44, to provide that the misoprostol used in the claims are in microgram amounts rather than milligram amounts. Support for this amendment is found at page 6 of the application, the prior use of milligrams having not had support in the application. This was a clerical error not previous found by the Applicants, nor objected to by the Examiner. Likewise, Applicant notes that the first Declaration of the inventor submitted with Applicant's response of October 20, 2010, also included the clerical error. Applicant has provided a new Declaration herewith that clearly indicates "micrograms" of misoprostol, not milligrams.

Turning to the rejections, the Examiner has continued to maintain the rejection of claims 40-55 under 35 U.S.C. 103(a) as being obvious and, therefore, unpatentable over Kirschner et al. U.S. Patent No. 6,899,890 ('Kirschner") in combination with Herschler U.S. Patent No. 4,997,823 ("Herschler") and Kelly International Patent Publication No. WO 02/092097 ("Kelly").

The Examiner has acknowledged the Declaration of the inventor, but notes that the amount of misoprostol to azithromycin administered is much lower than in the data previously presented. The Examiner further asserts that the Declaration is not found persuasive.

In response, the Applicant again notes that the claims as presently claimed refer to the vaginal administration of about 250 milligrams to about 1000 milligrams of azithromycin and 50 micrograms to about 1000 micrograms of misoprostol. In this connection, the combined delivery of azithromycin and misoprostol in the aforementioned quantities achieves a synergistic effect which results in higher than expected concentrations of azithromycin being absorbed into vaginal tissue and thereby provides unexpectedly improved treatment of pelvic tissue infection and the reduction of surgical trauma resulting from a gynaecological operation. Accordingly, the prevent invention is not obvious over a combination of Kelly and Kirschner, because an unexpected synergistic effect is observed.

In the Office Advisory Action of October 29, 2010, the Examiner argued that there was not sufficient evidence to demonstrate the aforementioned synergistic effect across the full range of amounts and ratio of azithromycin and misoprostol claimed. In this regard,

the Examples in the specification relate to a pessary formulation of 500 milligrams azithromycin and 400 micrograms misoprostol. (See page 10 of the specification). 100 of said pessary formulations were prepared using a total of 50 grams of azithromycin powder and 40 milligrams misoprostol (200 times 200 micrograms tablets), which was then divided into 100 molds, resulting in pessaries each containing 500 milligrams azithromycin and 400 micrograms misoprostol. The same said pessaries were used in Pilot Study II, wherein it was found that very high levels of azithromycin were present in the tissues compared to Pilot Study I in which azithromycin was administered alone.

Moreover, the Declaration of the inventor Dr Hazem El-Refaey provides further evidence in support of the synergistic effect between azithromycin and misoprostol. In this connection, the synergistic effect between azithromycin and misoprostol is believed to derive from the collagenolytic activity of misoprostol on vaginal tissue. (See paragraph 7 of the present Declaration). The collagenolytic activity of misoprostol helps to break apart collagen at the site of administration and thereby increases the porosity of the vaginal tissue to more easily absorb azithromycin.

While additional human clinical trials of the kind required to further directly support the synergistic effect between azithromycin and misoprostol at a variety of amounts and ratios are not immediately available (without organizing more human trials, which would take several years), Applicant is able to provide evidence of the collagenolytic activity in misoprostol and related prostaglandins on vaginal tissue. Applicant, therefore, submits that this evidence should be considered as supporting the Example of the specification which directly demonstrates a synergistic effect of azithromycin and misoprostol.

In this regard, European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 123 (2005) pages 62-66 "*Light-induced Fluorescence of the Human Cervix Decreases After Prostaglandin Application for Induction of Labor at Term*", provides evidence in support of the collagenolytic properties of misoprostol when administered vaginally in an amount of 50 micrograms.

In the final paragraph of page 63 of this document, it is stated that "twenty-five of the subjects received a half tablet of Cytotec® (misoprostol = 50 micrograms PGE1) from G.D. Searle & Co. intravaginally", while "16 subjects received Prepedil® gel (dinoprostone =

500 micrograms PGE2 (a prostaglandin having a similar collagenolytic activity as misoprostol)) from Pharmacia & Upjohn intracervically". Light induced fluroescence (LIF) (which is an index of cross-linked collagen) was measured for each participant.

The results on page 64 show that the LIF ratio of cervical collagen in all participants decreased significantly after administration of prostaglandin (specifically including misoprostol). Accordingly, it is concluded that cervical application of prostaglandins (specifically including misoprostol) decreases the amount of cross linked collagen.

In the third paragraph on page 63 of this paper, it is stated that "soluble collagen has less cross-links and therefore less fluroescence than insoluble collagen". Thus, it can quite reasonably be concluded from this paper that 50 micrograms of misoprostol, or 500 micrograms of dinoprostone, increases the solubility of vaginal tissue, which will lead to an increased absorption of azithromycin and the synergistic effect of the present invention.

European Journal of Obstetrics & Gynecology and Reproductive Biology, Vol. 67, No. 5, page 633-636 "*Cervical Collagen: An Important Regulator of Cervical Function in Term Labor*" provides still further evidence in support of the collagenolytic properties of prostaglandins when administered vaginally in an amount of 500 micrograms. In this paper, three groups of women A, B and C were studied. Group A were ten women with favourable cervixes and spontaneous labour. Group B were 12 women with unfavourable cervixes which were induced to labor with 500 micrograms of prostaglandin E2 in gel intracervically. Group C were five women with unfavourable cervixes and spontaneous but prolonged labor.

In the Results section on page 634, it is stated that "the total cervical collagen content was significantly higher in women in group C, 8.58 μg/mg compared to 6.7 μg/mg for women in Group A and 5.47 μg/mg for the prostaglandin E2 treated women in Group B. Accordingly, the collagenolytic activity was significantly increased in cervical biopsy specimens form prostaglandin E2 gel-treated patients (see abstract).

Applicant further asserts that the evidence proffered is commensurate in scope with the claimed invention. Applicants refer to M.P.E.P. §2145, wherein the MPEP quite clearly states that "Office personnel should not require the applicant to show unexpected results over the entire range of properties by a chemical compound or composition". Moreover, "a

showing of unexpected results for a single member of a claimed subgenus or a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof".

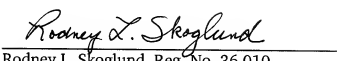
In this connection, Applicant has provided direct evidence of a synergistic effect between 500 milligrams azithromycin and 400 micrograms misoprostol. Applicant has also provided evidence in support of the causation of the synergistic effect, the collagenolytic activity of misoprostol at 50 micrograms. Applicant has further provided two pieces of evidence demonstrating collagenolytic activity of a related prostaglandin E2 at 500 micrograms. Moreover, the Declaration of Hazem El-Refaey further supports that a person of ordinary skill in the art, being provided with the teaching of the present application, would fully understand that the synergistic effect demonstrated at the probative amounts of 500 milligrams azithromycin and 400 micrograms misoprostol could be extended across the full range of 250 to 1000 milligrams azithromycin and 50 to 1000 micrograms misoprostol. The applicant is not attempting to unfairly claim a wide unsubstantiated range of amounts of drug. The claimed values are justified and scientifically derived. Indeed there is no reason to suspect on a balance of probabilities that, if a collagenolytic effect is seen for 50 micrograms, 400 micrograms and 500 micrograms of prostaglandin, that the resulting synergism with azithromycin would not be achievable across the full claimed range.

One of skill in the art would not have expected this result. Clearly, based upon the evidence now of record, the present claims are believed allowable over the cited prior art.

In light of the foregoing, reconsideration of all pending claims 40-55 is respectfully requested, and a Notice of Allowance of those claims is earnestly solicited. Should the Examiner wish to discuss any of the foregoing in greater detail, the undersigned attorney would welcome a telephone call.

In the event that a fee required for the filing of this document is missing or insufficient, the undersigned attorney hereby authorizes the Commissioner to charge payment of any fees associated with this communication or to credit any overpayment to Deposit Account No. **18-0987**.

Respectfully submitted,



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